ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each vial contains 10 ml of solution for injection, equivalent to 1000 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in vial.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues. See section 5.1 (Pharmacodynamics).

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

In the absence of compatibility studies, insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

Continuous subcutaneous infusion pump

When used with an insulin infusion pump, Apidra must not be mixed with diluents or any other insulin.

For further details on handling, see section 6.6.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Switching a patient to another type or brand of insulin should be done under strict medical supervision and may require change in dose.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.
Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin.

Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.
Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to <1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insuline glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 U/kg, and less than proportional increase in glucose lowering effect with 0.3 U/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine

administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

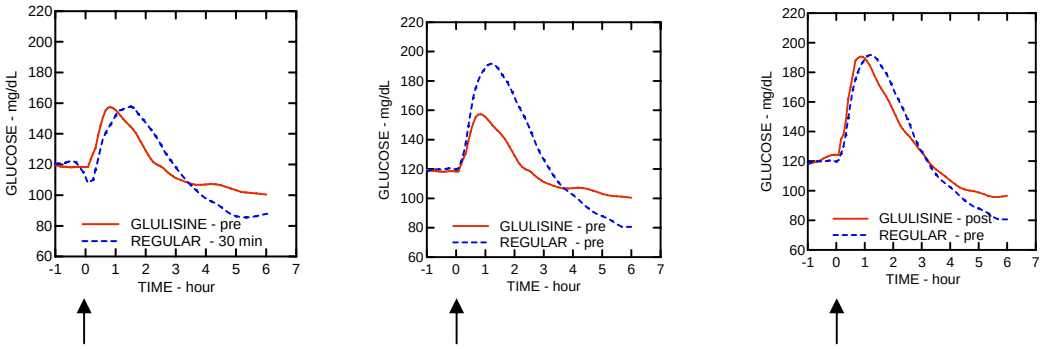

Figure 1 A Figure 1B Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427mg.kg^{-1} for insulin glulisine, 121 minutes and 354mg.kg^{-1} for lispro, 150 minutes and 197mg.kg^{-1} for regular human insulin (see figure 2).

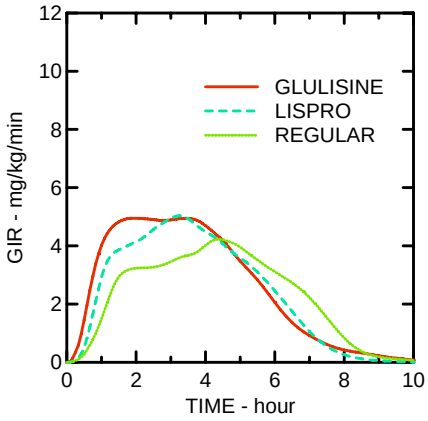

Figure 2: Glucose infusion rates after subcutaneous injection of 0.3 U/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices, while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 U/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 U/kg insulin lispro respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI:0.81, 0.95 (p=<0.01)]has shown that insulin glulisine effectively controls diurnal post-prandial blood glucose excursions.

Clinical studies

Type 1 diabetes mellitus
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 2 diabetes mellitus
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58 % of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and Gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4U/kg.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 U/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µU/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µU/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure3).

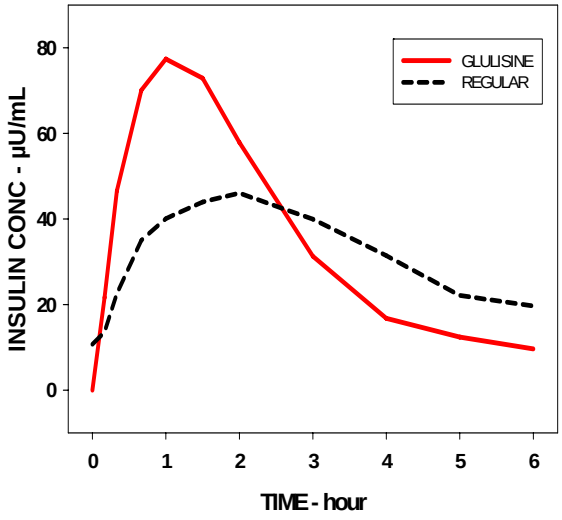

Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellituspatients after a dose of 0.15 U/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 U/kg insulin glulisine, the Cmax was 91 µU/ml with the interquartile range from 78 to 104 µU/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV).

Obesity

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices.

The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801$mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

When used with an insulin infusion pump, Apidra must not be mixed with other medicinal products.

6.3 Shelf life

2 years.

Shelf life after first use: the product may be stored for a maximum of 4 weeks not above 25°C.Keep the vial in the outer carton in order to protect from light.

6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C - 8°C)
Keep the vial in the outer carton in order to protect from light.
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:

For storage precautions, see section 6.3.

6.5 Nature and contents of container

10 ml solution in a vial (type I colourless glass) with a stopper (flanged aluminium overseal, elastomeric rubber) and tear-off lid. Packs of 1, 2, 4 and 5 vials are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Apidra vials are for use with insulin syringes with the corresponding unit scale and for use with an insulin pump system (see section 4.2).

Inspect the vial before use. It must only be used if the solution is clear, colourless, with no solid particles visible. Since Apidra is a solution, it does not require resuspension before use.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

Continuous subcutaneous infusion pump

Apidra may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems suitable for insulin infusion with the appropriate catheters and reservoirs.

Patients using CSII should be comprehensively instructed on the use of the pump system. The infusion set and reservoir should be changed every 48 hours using aseptic technique.

Patients administering Apidra by CSII must have alternative insulin available in case of pump system failure.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/001-004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in cartridge.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each cartridge contains 3 ml of solution for injection, equivalent to 300 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in cartridge.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues. See section 5.1 (Pharmacodynamics).

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

In the absence of compatibility studies, insulin glulisine must not be mixed with other medicinal products except NPH human insulin.
For further details on handling, see section 6.6.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Switching a patient to another type or brand of insulin should be done under strict medical supervision and may require change in dose.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.
Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to<1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.
There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insuline glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 U/kg, and less than proportional increase in glucose lowering effect with 0.3 U/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to

regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

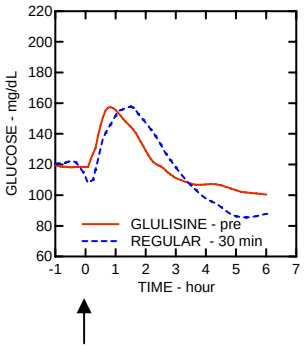

Figure 1 A

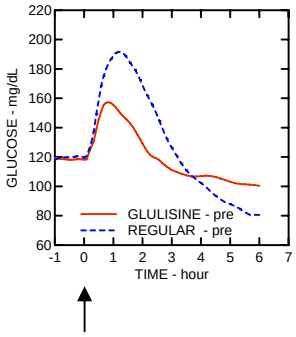

Figure 1B

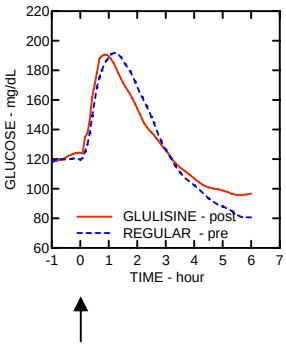

Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427mg.kg^{-1} for insulin glulisine, 121 minutes and 354mg.kg^{-1} for lispro, 150 minutes and 197mg.kg^{-1} for regular human insulin (see figure 2).

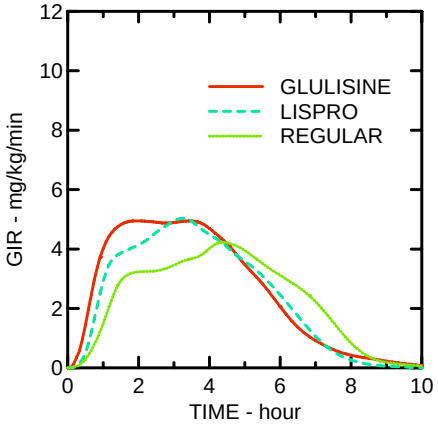

Figure 2: Glucose infusion rates after subcutaneous injection of 0.3 U/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices, while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 U/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 U/kg insulin lispro respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI:0.81, 0.95 (p=<0.01)]has shown that insulin glulisine effectively controls diurnal post-prandial blood glucose excursions.
Clinical studies

Type 1 diabetes mellitus
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 2 diabetes mellitus
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58 % of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and Gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4U/kg.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 U/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 µU/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 µU/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure 3).

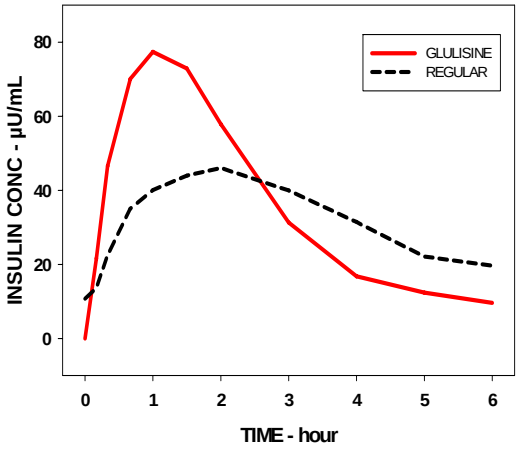

Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 U/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 U/kg insulin glulisine, the Cmax was 91 µU/ml with the interquartile range from 78 to 104 µU/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV).

Obesity

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices.

The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801$mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

6.3 Shelf life

2 years.
Shelf life after first use: the product may be stored for a maximum of 4 weeks not above 25°C. Do not refrigerate. Keep the cartridge inserted in the pen protected from light.

6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C - 8°C).
Keep the cartridge in the outer carton in order to protect from light.
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
For storage precautions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (type I colourless glass) with a plunger (elastomeric rubber) and an overseal (flanged aluminium) with a stopper (elastomeric rubber). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The cartridges are to be used in conjunction with an insulin pen such as OptiPen and as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection. Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible. Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen). Empty cartridges must not be refilled.

If OptiPen is damaged, it should not be used.

If the pen malfunctions, the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 Units/ml) and injected.

To prevent any kind of contamination, the re-usable pen should be used by a single patient only.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/005-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in cartridge.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each cartridge contains 3 ml of solution for injection, equivalent to 300 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in cartridge for OptiClik.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues. See section 5.1 (Pharmacodynamics).

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

In the absence of compatibility studies, insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

For further details on handling, see section 6.6.

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Switching a patient to another type or brand of insulin should be done under strict medical supervision and may require change in dose.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.
Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.

Insulin requirements may be altered during illness or emotional disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery). Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to<1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions
Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes.

Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insuline glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 U/kg, and less than proportional increase in glucose lowering effect with 0.3 U/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at

different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

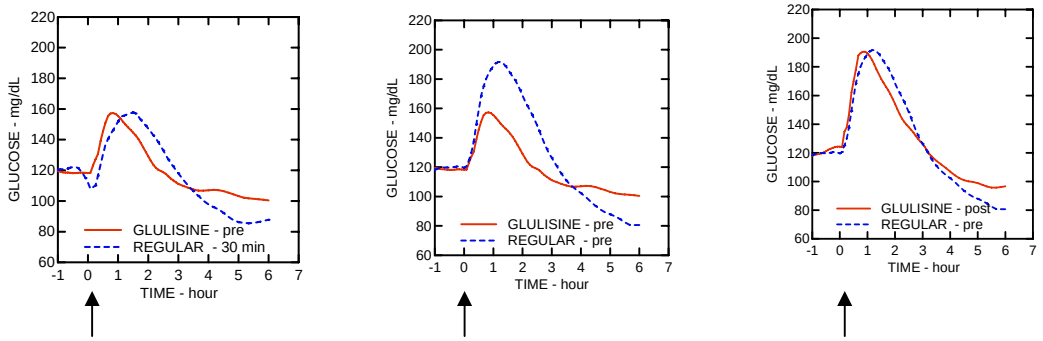

Figure 1 A Figure 1B Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427mg.kg^{-1} for insulin glulisine, 121 minutes and 354mg.kg^{-1} for lispro, 150 minutes and 197mg.kg^{-1} for regular human insulin (see figure 2).

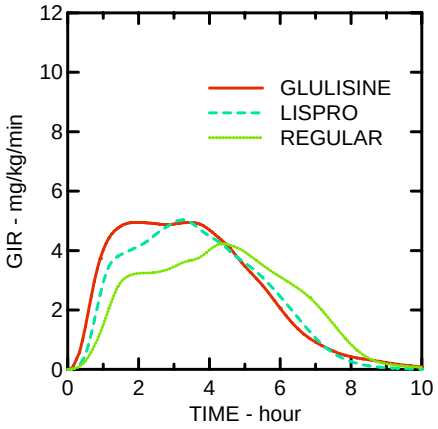

Figure 2: Glucose infusion rates after subcutaneous injection of 0.3 U/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

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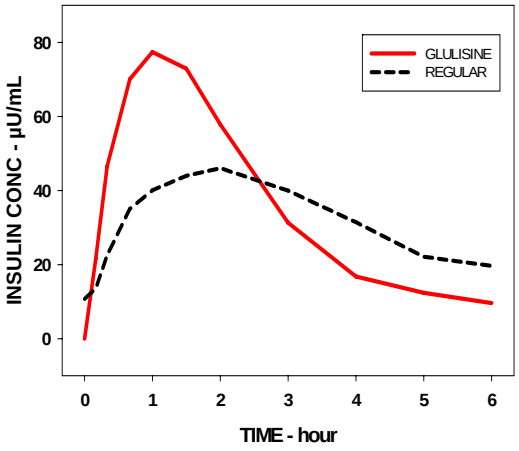

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The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

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The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801$mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

6.3 Shelf life

2 years.

Shelf life after first use: the product may be stored for a maximum of 4 weeks not above 25°C.Do not refrigerate. Keep the cartridge inserted in the pen protected from light.

6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C - 8°C).
Keep the cartridge in the outer carton in order to protect from light.
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
For storage precautions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (type I colourless glass cartridge) with a plunger (elastomeric rubber) and a overseal (flanged aluminium) with a stopper (elastomeric rubber).

The glass cartridge is irreversibly integrated in a transparent container and attached to a plastic mechanism by a threaded rod at one extremity.

Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges for OptiClik are available. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The cartridges for OptiClik are to be used in conjunction with OptiClik only, and as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection.

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used.

Before insertion of the cartridge into the reusable pen, the cartridge must be stored at room temperature for 1 to 2 hours. Inspect the cartridge before use. It must only be used if the cartridge is intact and the solution is clear, colourless, with no solid particles visible.
Air bubbles must be removed from the cartridge before injection (see instruction for using pen). Empty cartridges must not be refilled.

If the pen malfunctions,(see instructions for using the pen) the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 Units/ml) and injected.

To prevent any kind of contamination, the re-usable pen should be used by a single patient only.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/021-028

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each pen contains 3 ml of solution for injection, equivalent to 300 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen. OptiSet.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues. See section 5.1 (Pharmacodynamics).

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall,thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.

Mixing with insulins

In the absence of compatibility studies, insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

Before using OptiSet, the Instructions for Use included in the Package Leaflet must be read carefully (see section 6.6).

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Switching a patient to another type or brand of insulin should be done under strict medical supervision and may require change in dose.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.
Insulin requirements may be altered during illness or emotional disturbances.

Handling of the pen
Before using OptiSet, the Instructions for Use included in the Package Leaflet must be read carefully. OptiSet has to be used as recommended in these Instructions for Use (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to<1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions

Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insuline glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 U/kg, and less than proportional increase in glucose lowering effect with 0.3 U/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

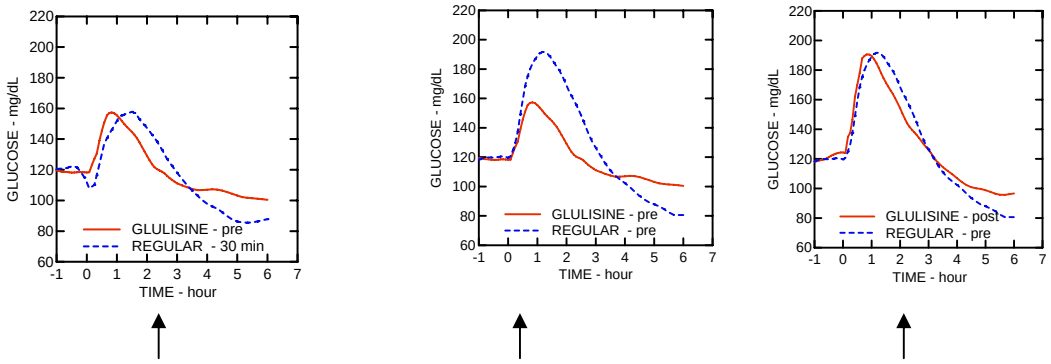
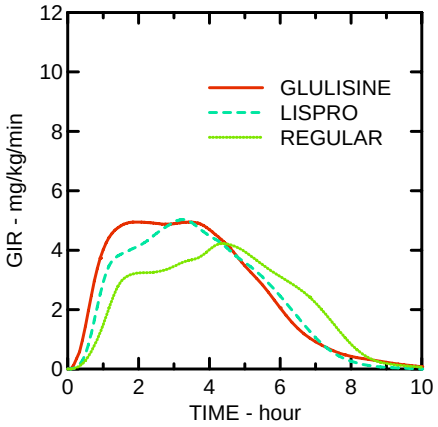


Figure 1 A Figure 1B Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427mg.kg^{-1} for insulin glulisine, 121 minutes and 354mg.kg^{-1} for lispro, 150 minutes and 197mg.kg^{-1} for regular human insulin (see figure 2).



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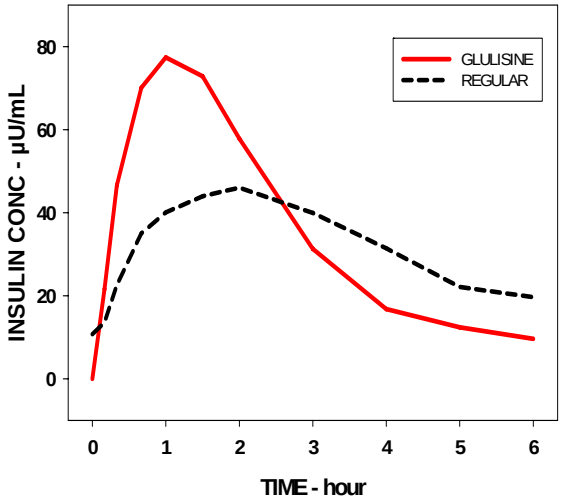

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Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

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Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801$mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

6.3 Shelf life

2 years.

Shelf life after first use: the product may be stored for a maximum of 4 weeks not above 25°C. Keep the pre-filled pen in the outer carton in order to protect from light.
Do not refrigerate.

6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C - 8°C).
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:
For storage precautions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (colourless glass) with a plunger (elastomeric rubber) and an overseal (flanged aluminium) with a stopper (elastomeric rubber). The cartridge is sealed in a disposable pre-filled pen. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pens are available.

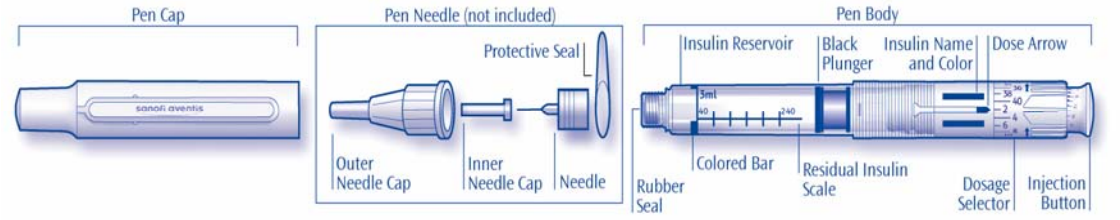
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Apidra is a solution, it does not require resuspension before use.

Empty pens must never be used and must be properly discarded.
To prevent any kind of contamination, the use of the pre-filled pen should remain strictly for a single patient use.

Handling of the pen
The Instructions for Use included in the Package Leaflet must be read carefully before using OptiSet.



Schematic diagram of the pen

Important information for use of OptiSet:
- Always attach a new needle before each use. Only use needles that are compatible for use with OptiSet.
- Always perform the safety test before each injection.
- If a new OptiSet is used the initial safety test must be done with the 8 units preset by the manufacturer.
- The dosage selector can only be turned in one direction.
- Never turn the dosage selector (change the dose) after injection button has been pulled out.
- This pen is only for the patients use. It must not be shared with anyone else.
- If the injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use OptiSet if it is damaged or if you are not sure that it is working properly.
- Always have a spare OptiSet in case your OptiSet is lost or damaged.

Storage Instructions

Please check section 6.4 of this leaflet for instructions on how to store OptiSet.

If OptiSet is in cool storage, it should be taken out 1 to 2 hours before injection to allow it to warm up. Cold insulin is more painful to inject.

The used OptiSet must be discarded as required by your local authorities.

Maintenance

OptiSet has to be protected from dust and dirt.

You can clean the outside of your OptiSet by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

OptiSet is designed to work accurately and safely. It should be handled with care. Avoid situations where OptiSet might be damaged. If you are concerned that your OptiSet may be damaged, use a new one.

Step 1 Check the Insulin

After removing the pen cap, the label on the pen and the insulin reservoir should be checked to make sure it contains the correct insulin. The appearance of insulin should also be checked: the insulin solution must be clear, colourless, with no solid particles visible, and must have a water-like consistency. Do not use this OptiSet if the insulin is cloudy, coloured or has particles.

Step 2 Attach the needle

The needle should be carefully attached straight onto the pen.

Step 3 Perform a safety test

Prior to each injection a safety test has to be performed.

For a new and unused OptiSet, a dose of 8 units is already preset by the manufacturer for the first safety test.

In-use OptiSet, select a dose of 2 units by turning the dosage selector forward till the dose arrow points to 2. The dosage selector will only turn in one direction.
Pull out the injection button completely in order to load the dose. Never turn the dosage selector after injection button has been pulled out.
The outer and inner needle caps should be removed. Keep the outer cap to remove the used needle.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed all the way in .

If insulin has been expelled through the needle tip, then the pen and the needle are working properly. If no insulin appears at the needle tip, step 3 should be repeated two more times until insulin appears at the needle tip. If still no insulin comes out, change the needle, as it might be blocked and try again. If no insulin comes out after changing the needle, the OptiSet may be damaged. Do not use this OptiSet.

Step 4 Select the dose

The dose can be set in steps of 2 units, from a minimum of 2 units to a maximum of 40 units. If a dose greater than 40 units is required, it should be given as two or more injections.

Check if you have enough insulin for the dose.

The residual insulin scale on the transparent insulin reservoir shows approximately how much insulin remains in the OptiSet. This scale must not be used to set the insulin dose.
If the black plunger is at the beginning of the coloured bar, then there are approximately 40 units of insulin available.
If the black plunger is at the end of the coloured bar, then there are approximately 20 units of insulin available.

The dosage selector should be turned forward until the dose arrow points to the required dose.

Step 5 Load the dose

The injection button should be pulled out as far as it will go in order to load the pen.

Check if the selected dose is fully loaded. Note that the injection button only goes out as far as the amount of insulin that is left in the reservoir.

The injection button allows checking the actual loaded dose. The injection button must be held out under tension during this check. The last thick line visible on the injection button shows the amount of insulin loaded. When the injection button is held out only the top part of this thick line can be seen.

Step 6. Inject the dose

The patient should be informed on the injection technique by his health care professional.
The needle should be inserted into the skin

The injection button should be pressed all the way in . A clicking sound can be heard, which will stop when the injection button has been pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle from the skin. This ensures that the full dose of insulin has been delivered..

Step 7 Remove and discard the needle

The needle should be removed after each injection and discarded. This helps prevent contamination and/or infection as well as entry of air into the insulin reservoir and leakage, of the insulin, which can cause inaccurate dosing . Needles must not be reused.

The pen cap should be replaced on the pen.

Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/013-020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in a pre-filled pen.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 100 Units insulin glulisine (equivalent to 3.49 mg).

Each pen contains 3 ml of solution for injection, equivalent to 300 Units.

Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli*.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection in a pre-filled pen. SoloStar.

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with diabetes mellitus.

4.2 Posology and method of administration

The potency of this preparation is stated in units. These units are exclusive to Apidra and are not the same as IU or the units used to express the potency of other insulin analogues. See section 5.1 (Pharmacodynamics).

Apidra should be given shortly (0-15 min) before or soon after meals.

Apidra should be used in regimens that include an intermediate or long acting insulin or basal insulin analogue and can be used with oral hypoglycaemic agents.

The dosage of Apidra should be individually adjusted.

Administration

Apidra should be given by subcutaneous injection or by continuous subcutaneous pump infusion.

Apidra should be administered subcutaneously in the abdominal wall, thigh or deltoid or by continuous infusion in the abdominal wall. Injection sites and infusion sites within an-injection area (abdomen, thigh or deltoid) should be rotated from one injection to the next. The rate of absorption, and consequently the onset and duration of action, may be affected by the injection site, exercise and other variables. Subcutaneous injection in the abdominal wall ensures a slightly faster absorption than other injection sites (see section 5.2).

Care should be taken to ensure that a blood vessel has not been entered. After injection, the site of injection should not be massaged. Patients must be educated to use proper injection techniques.
Mixing with insulins

In the absence of compatibility studies, insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully (see section 6.6).

Special populations

Renal impairment
The pharmacokinetic properties of insulin glulisine are generally maintained in patients with renal impairment. However, insulin requirements may be reduced in the presence of renal impairment (see section 5.2).

Hepatic impairment
The pharmacokinetic properties of insulin glulisine have not been investigated in patients with decreased liver function. In patients with hepatic impairment, insulin requirements may be diminished due to reduced capacity for gluconeogenesis and reduced insulin metabolism.

Elderly
Limited pharmacokinetic data are available in elderly patients with diabetes mellitus. Deterioration of renal function may lead to a decrease in insulin requirements.

Children and adolescents
There is no adequate clinical information on the use of Apidra in children and adolescents.

4.3 Contraindications

Hypersensitivity to insulin glulisine or to any of the excipients.

Hypoglycaemia.

4.4 Special warnings and precautions for use

Transferring a patient to a new type or brand of insulin should be done under strict medical supervision. Changes in strength, brand (manufacturer), type (regular, NPH, lente, etc.), species (animal) and/or method of manufacturing may result in a change in dosage. Concomitant oral antidiabetic treatment may need to be adjusted.

The use of inadequate dosages or discontinuation of treatment, especially in insulin-dependent diabetic, may lead to hyperglycaemia and diabetic ketoacidosis; conditions which are potentially lethal.

Switching a patient to another type or brand of insulin should be done under strict medical supervision and may require change in dose.

Hypoglycaemia
The time of occurrence of hypoglycaemia depends on the action profile of the insulins used and may, therefore, change when the treatment regimen is changed.

Conditions which may make the early warning symptoms of hypoglycaemia different or less pronounced include long duration of diabetes, intensified insulin therapy, diabetic nerve disease, medicinal products such as beta blockers or after transfer from animal-source insulin to human insulin. Adjustment of dosage may be also necessary if patients undertake increased physical activity or change their usual meal plan. Exercise taken immediately after a meal may increase the risk of hypoglycaemia.

When compared with soluble human insulin, if hypoglycaemia occurs after an injection with rapid acting analogues, it may occur earlier.

Uncorrected hypoglycaemic or hyperglycaemic reactions can cause loss of consciousness, coma, or death.
Insulin requirements may be altered during illness or emotional disturbances.

Handling of the pen
Before using SoloStar, the Instructions for Use included in the Package Leaflet must be read carefully. SoloStar has to be used as recommended in these Instructions for Use (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

Studies on pharmacokinetic interactions have not been performed. Based on empirical knowledge from similar medicinal products, clinically relevant pharmacokinetic interactions are unlikely to occur.

A number of substances affect glucose metabolism and may require dose adjustment of insulin glulisine and particularly close monitoring.

Substances that may enhance the blood-glucose-lowering activity and increase susceptibility to hypoglycaemia include oral antidiabetic agents, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamide oxidase inhibitors (MAOIs), pentoxifylline, propoxyphene, salicylates and sulfonamide antibiotics.

Substances that may reduce the blood-glucose-lowering activity include corticosteroids, danazol, diazoxide, diuretics, glucagon, isoniazid, phenothiazine derivatives, somatropin, sympathomimetic agents (e.g. epinephrine [adrenaline], salbutamol, terbutaline), thyroid hormones, estrogens, progestins (e.g. in oral contraceptives), protease inhibitors and atypical antipsychotic medicinal products (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts or alcohol may either potentiate or weaken the blood-glucose-lowering activity of insulin. Pentamidine may cause hypoglycaemia, which may sometimes be followed by hyperglycaemia.

In addition, under the influence of sympatholytic medicinal products such as beta-blockers, clonidine, guanethidine and reserpine, the signs of adrenergic counter-regulation may be reduced or absent.

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of insulin glulisine in pregnant women.

Animal reproduction studies have not revealed any differences between insulin glulisine and human insulin regarding pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).

Caution should be exercised when prescribing to pregnant women. Careful monitoring of glucose control is essential.

It is essential for patients with pre-existing or gestational diabetes to maintain good metabolic control throughout pregnancy. Insulin requirements may decrease during the first trimester and generally increase during the second and third trimesters. Immediately after delivery, insulin requirements decline rapidly.

Lactation

It is unknown whether insulin glulisine is excreted in human milk, but in general insulin does not pass into breast milk and is not absorbed after oral administration.

Breast-feeding mothers may require adjustments in insulin dose and diet.

4.7 Effects on ability to drive and use machines

The patient's ability to concentrate and react may be impaired as a result of hypoglycaemia or hyperglycaemia or, for example, as a result of visual impairment. This may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

Patients should be advised to take precautions to avoid hypoglycaemia whilst driving. This is particularly important in those who have reduced or absent awareness of the warning symptoms of hypoglycaemia or have frequent episodes of hypoglycaemia. The advisability of driving should be considered in these circumstances.

4.8 Undesirable effects

Hypoglycaemia, the most frequent undesirable effect of insulin therapy, may occur if the insulin dose is too high in relation to the insulin requirement.

The following related adverse reactions from clinical investigations were listed below by system organ class and in order of decreasing incidence (very common: ≥1/10; common: ≥1/100 to<1/10; uncommon: ≥ 1/1,000 to < 1/100; rare: ≥1/10,000 to <1/1,000; very rare: < 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Metabolism and nutrition disorders
Very common: Hypoglycaemia
Symptoms of hypoglycaemia usually occur suddenly. They may include cold sweats, cool pale skin, fatigue, nervousness or tremor, anxiousness, unusual tiredness or weakness, confusion, difficulty in concentration, drowsiness, excessive hunger, vision changes, headache, nausea and palpitation. Hypoglycaemia can become severe and may lead to unconsciousness and/or convulsions and may result in temporary or permanent impairment of brain function or even death.

Skin and subcutaneous tissue disorders
Common: injection site reactions and local hypersensitivity reactions.
Local hypersensitivity reactions (redness, swelling and itching at the injection site) may occur during treatment with insulin. These reactions are usually transitory and normally they disappear during continued treatment.

Rare: Lipodystrophy
Lipodystrophy may occur at the injection site as a consequence of failure to rotate injection sites within an area.

General disorders
Uncommon: Systemic hypersensitivity reactions

Systemic hypersensitivity reactions may include urticaria, chest tightness, dyspnea, allergic dermatitis and pruritus. Severe cases of generalized allergy, including anaphylactic reaction, may be life-threatening.

4.9 Overdose

Hypoglycaemia may occur as a result of an excess of insulin activity relative to food intake and energy expenditure.

There are no specific data available concerning overdose with insulin glulisine. However, hypoglycaemia may develop over sequential stages:

Mild hypoglycaemic episodes can be treated by oral administration of glucose or sugary products. It is therefore recommended that the diabetic patient constantly carries some sugar lumps, sweets, biscuits or sugary fruit juice.

Severe hypoglycaemic episodes, where the patient has become unconscious, can be treated by glucagon (0.5 to 1 mg) given intramuscularly or subcutaneously by a person who has received appropriate instruction, or by glucose given intravenously by a medical professional. Glucose must also be given intravenously, if the patient does not respond to glucagon within 10 to 15 minutes. Upon regaining consciousness, administration of oral carbohydrate is recommended for the patient in order to prevent relapse.
After an injection of glucagon, the patient should be monitored in a hospital in order to find the reason for this severe hypoglycaemia and prevent other similar episodes.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: insulin and analogues, fast-acting. ATC code: A10AB06

Insulin glulisine is a recombinant human insulin analogue that is equipotent to regular human insulin. Insulin glulisine has a more rapid onset of action and a shorter duration of action than regular human insulin.

The primary activity of insulins and insulin analogues, including insulin glulisine, is regulation of glucose metabolism. Insulins lower blood glucose levels by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis in the adipocyte, inhibits proteolysis and enhances protein synthesis.

Studies in healthy volunteers and patients with diabetes demonstrated that insulin glulisine is more rapid in onset of action and of shorter duration of action than regular human insulin when given subcutaneously. When insuline glulisine is injected subcutaneously, the glucose lowering activity will begin within 10 – 20 minutes. The glucose-lowering activities of insulin glulisine and regular human insulin are equipotent when administered by intravenous route. One unit of insulin glulisine has the same glucose-lowering activity as one unit of regular human insulin.

Dose proportionality

In a study with 18 male subjects with diabetes mellitus type 1 aged 21 to 50 years, insulin glulisine displayed dose-proportional glucose lowering effect in the therapeutic relevant dose range 0.075 to 0.15 U/kg, and less than proportional increase in glucose lowering effect with 0.3 U/kg or higher, like human insulin.

Insulin glulisine takes effect about twice as fast as regular human insulin and completes the glucose lowering effect about 2 hours earlier than regular human insulin.

A phase I study in patients with type 1 diabetes mellitus assessed the glucose lowering profiles of insulin glulisine and regular human insulin administered subcutaneously at a dose of 0.15 U/kg, at different times in relation to a 15-minute standard meal. Data indicated that insulin glulisine administered 2 minutes before the meal gives similar postprandial glycemic control compared to regular human insulin given 30 minutes before the meal. When given 2 minutes prior to meal, insulin glulisine provided better postprandial control than regular human insulin given 2 minutes before the meal. Insulin glulisine administered 15 minutes after starting the meal gives similar glycemic control as regular human insulin given 2 minutes before the meal (see figure 1).

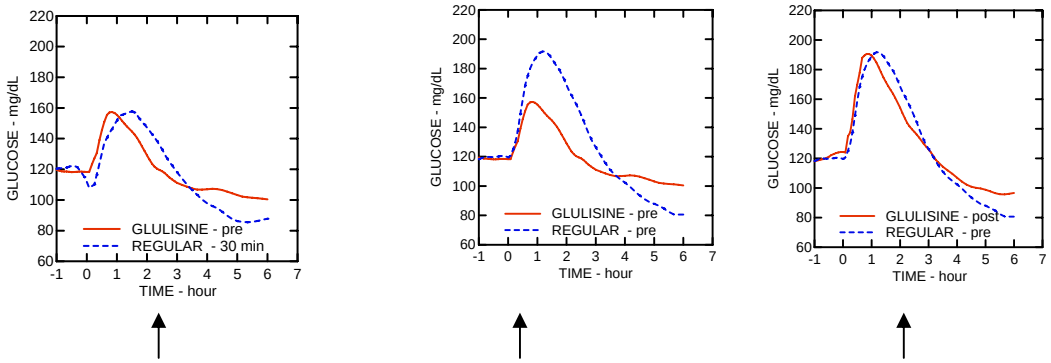


Figure 1 A Figure 1B Figure 1C

Figure 1: Average glucose-lowering effect over 6 hours in 20 patients with type 1 diabetes mellitus. Insulin glulisine given 2 minutes (GLULISINE pre) before the start of a meal compared to regular human insulin given 30 minutes (REGULAR 30 min) before the start of the meal (figure 1A) and compared to regular human insulin given 2 minutes (REGULAR pre) before a meal (figure 1B). Insulin glulisine given 15 minutes (GLULISINE post) after start of a meal compared to regular human insulin given 2 minutes (REGULAR pre) before start of the meal (figure 1C). On the x-axis, zero (arrow) is the start of a 15-minute meal.

Obesity

A phase I study carried out with insulin glulisine, lispro and regular human insulin in an obese population has demonstrated that insulin glulisine maintains its rapid-acting properties. In this study, the time to 20% of total AUC and the AUC (0-2h) representing the early glucose lowering activity were respectively of 114 minutes and 427mg.kg^{-1} for insulin glulisine, 121 minutes and 354mg.kg^{-1} for lispro, 150 minutes and 197mg.kg^{-1} for regular human insulin (see figure 2).

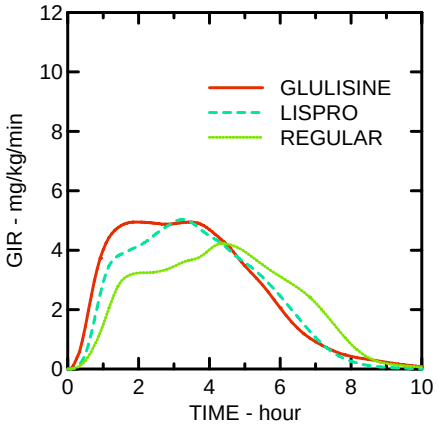


Figure 2: Glucose infusion rates after subcutaneous injection of 0.3 U/kg of insulin glulisine (GLULISINE) or insulin lispro (LISPRO) or regular human insulin (REGULAR) in an obese population.

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid action is generally maintained across a wide range of body mass indices, while total glucose lowering effect decreases with increasing obesity.

The average total GIR AUC between 0–1 hour was 102±75 mg/kg and 158±100 mg/kg with 0.2 and 0.4 U/kg insulin glulisine, respectively, and was 83.1±72.8 mg/kg and 112.3±70.8 mg/kg with 0.2 and 0.4 U/kg insulin lispro respectively.

A phase I study in 18 obese patients with type 2 diabetes mellitus (BMI between 35 and 40 kg/m^2) with insulin glulisine and insulin lispro [90% CI: 0.81, 0.95 (p=<0.01)] has shown that insulin glulisine effectively controls diurnal post-prandial blood glucose excursions.

Clinical studies

Type 1 diabetes mellitus
In a 26-week phase III clinical study comparing insulin glulisine with insulin lispro both injected subcutaneously shortly (0-15 minutes) before a meal in patients with type 1 diabetes mellitus using insulin glargine as basal insulin, insulin glulisine was comparable to insulin lispro for glycemic control as reflected by changes in glycated haemoglobin (expressed as HbA_{1c} equivalent) from baseline to endpoint. Comparable self-monitored blood glucose values were observed. No increase in the basal insulin dose was needed with insulin glulisine, in contrast to insulin lispro.

A 12-week phase III clinical study performed in patients with type 1 diabetes mellitus receiving insulin glargine as basal therapy indicate that the immediate postmeal administration of insulin glulisine provides efficacy that was comparable to immediate premeal insulin glulisine (0-15 minutes) or regular insulin (30-45 minutes).

In the per protocol population there was a significantly larger observed reduction in GHb in the premeal glulisine group compared with the regular insulin group.

Type 2 diabetes mellitus
A 26-week phase III clinical study followed by a 26-week extension safety study was conducted to compare insulin glulisine (0-15 minutes before a meal) with regular human insulin (30-45 minutes before a meal) injected subcutaneously in patients with type 2 diabetes mellitus also using NPH insulin as basal insulin. The average body mass index (BMI) of patients was 34.55 kg/m^2. Insulin glulisine was shown to be comparable to regular human insulin with regard to glycated haemoglobin (expressed as HbA_{1c} equivalent) changes from baseline to the 6-month endpoint (-0.46% for insulin glulisine and -0.30% for regular human insulin, p=0.0029) and from baseline to the 12-month endpoint (-0.23% for insulin glulisine and -0.13% for regular human insulin, difference not significant). In this study, the majority of patients (79%) mixed their short acting insulin with NPH insulin immediately prior to injection and 58 % of subjects used oral hypoglycemic agents at randomization and were instructed to continue to use them at the same dose.

Race and Gender
In controlled clinical trials in adults, insulin glulisine did not show differences in safety and efficacy in subgroup analyses based on race and gender.

5.2 Pharmacokinetic properties

In insulin glulisine the replacement of the human insulin amino acid asparagine in position B3 by lysine and the lysine in position B29 by glutamic acid favors more rapid absorption.

In a study with 18 male subjects with diabetes mellitus type 1, aged 21 to 50 years, insulin glulisine displays dose-proportionality for early, maximum and total exposure in the dose range 0.075 to 0.4U/kg.

Absorption and bioavailability

Pharmacokinetic profiles in healthy volunteers and diabetes patients (type 1 or 2) demonstrated that absorption of insulin glulisine was about twice as fast with a peak concentration approximately twice as high as compared to regular human insulin.

In a study in patients with type 1 diabetes mellitus after subcutaneous administration of 0.15 U/kg, for insulin glulisine the T_{max} was 55 minutes and C_{max} was 82 ± 1.3 □U/ml compared to a T_{max} of 82 minutes and a C_{max} of 46 ± 1.3 □U/ml for regular human insulin. The mean residence time of insulin glulisine was shorter (98 min) than for regular human insulin (161 min) (see figure3).

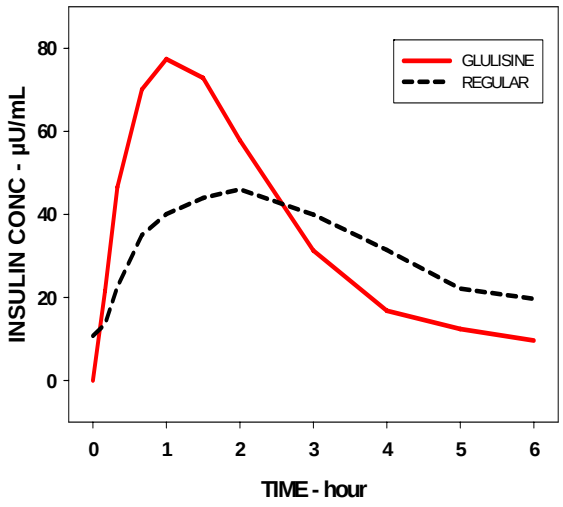


Figure 3: Pharmacokinetic profile of insulin glulisine and regular human insulin in type 1 diabetes mellitus patients after a dose of 0.15 U/kg.

In a study in patients with type 2 diabetes mellitus after subcutaneous administration of 0.2 U/kg insulin glulisine, the Cmax was 91 µU/ml with the interquartile range from 78 to 104 µU/ml.

When insulin glulisine was injected subcutaneously into abdomen, deltoid and thigh, the concentration-time profiles were similar with a slightly faster absorption when administered in the abdomen compared to the thigh. Absorption from deltoid sites was in-between (see section 4.2). The absolute bioavailability (70%) of insulin glulisine was similar between injection sites and of low intra-subject variability (11%CV).

Obesity

Another phase I study with insulin glulisine and insulin lispro in a non-diabetic population in 80 subjects with a wide range of body mass indices (18-46 kg/m²) has demonstrated that rapid absorption and total exposure is generally maintained across a wide range of body mass indices.

The time to 10% of total INS exposure was reached earlier by approximately 5–6 min with insulin glulisine.

Distribution and elimination

The distribution and elimination of insulin glulisine and regular human insulin after intravenous administration is similar with volumes of distribution of 13 l and 22 l and half-lives of 13 and 18 minutes, respectively.

After subcutaneous administration, insulin glulisine is eliminated more rapidly than regular human insulin with an apparent half-life of 42 minutes compared to 86 minutes. In an across study analysis of insulin glulisine in either healthy subjects or subjects with type 1 or type 2 diabetes mellitus the apparent half-life ranged from 37 to 75 minutes (interquartile range).

Insulin glulisine shows low plasma protein binding, similar to human insulin.

Special populations

Renal impairment
In a clinical study performed in non-diabetic subjects covering a wide range of renal function (CrCl > 80 ml/min, 30-50 ml/min, < 30 ml/min), the rapid-acting properties of insulin glulisine were generally maintained. However, insulin requirements may be reduced in the presence of renal impairment.

Hepatic impairment
The pharmacokinetic properties have not been investigated in patients with impaired liver function.

Elderly
Very limited pharmacokinetic data are available for elderly patients with diabetes mellitus.

Children and adolescents
The pharmacokinetic and pharmacodynamic properties of insulin glulisine were investigated in children (7-11 years) and adolescents (12-16 years) with type 1 diabetes mellitus. Insulin glulisine was rapidly absorbed in both age groups, with similar T_{max} and C_{max} as in adults (see section 4.2). Administered immediately before a test meal, insulin glulisine provided better postprandial control than regular human insulin, as in adults (see section 5.1). The glucose excursion (AUC_{0-6h}) was 641 $mg.h.dl^{-1}$ for insulin glulisine and 801$mg.h.dl^{-1}$ for regular human insulin.

5.3 Preclinical safety data

Non-clinical data did not reveal toxicity findings others than those linked to the blood glucose lowering pharmacodynamic activity (hypoglycemia), different from regular human insulin or of clinical relevance for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Metacresol
Sodium chloride
Trometamol
Polysorbate 20
Hydrochloric acid, concentrated
Sodium hydroxide
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies insulin glulisine must not be mixed with other medicinal products except NPH human insulin.

6.3 Shelf life

2 years.

Shelf life after first use: the product may be stored for a maximum of 4 weeks not above 25°C. Do not refrigerate.
Keep the pen protected from light.

6.4 Special precautions for storage

Unopened
Store in a refrigerator (2°C-8°C). Keep the pre-filled pen in the outer carton in order to protect from light. Do not freeze. Ensure that the pen is not directly touching the freezer compartment or freezer packs.

Before first use, the pen must be stored at room temperature for 1 to 2 hours.

In use conditions
For storage precautions, see section 6.3.

6.5 Nature and contents of container

3 ml solution in a cartridge (colourless glass) with a plunger (elastomeric rubber) and an overseal (flanged aluminium) with a stopper (elastomeric rubber). The cartridge is sealed in a disposable pre-filled pen. Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pens are available.

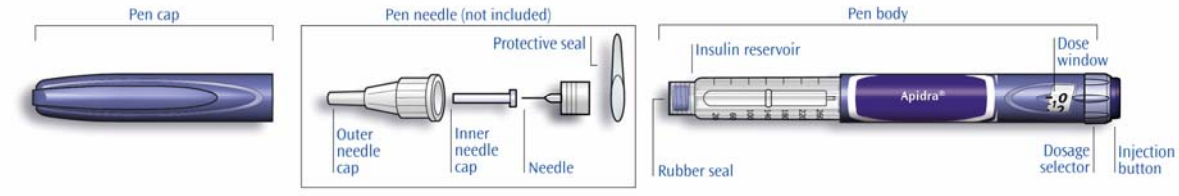
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Inspect the cartridge before use. It must only be used if the solution is clear, colourless, with no solid particles visible, and if it is of water-like consistency. Since Apidra is a solution, it does not require resuspension before use.

Empty pens must never be used and must be properly discarded.
To prevent any kind of contamination, the use of the pre-filled pen should remain strictly for a single patient use.

Handling of the pen
The Instructions for Use included in the Package Leaflet must be read carefully before using SoloStar.



Schematic diagram of the pen

Important information for use of SoloStar:

Before each use, a new needle must always be carefully attached and a safety test must be performed.
Only use needles that are compatible for use with SoloStar.
Special caution must be taken to avoid accidental needle injury and transmission of infection.
Never use SoloStar if it is damaged or if you are not sure that it is working properly.
Always have a spare SoloStar in case your SoloStar is lost or damaged.

Storage Instructions

Please check section 6.4 for instructions on how to store SoloStar.

If SoloStar is in cool storage, it should be taken out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

The used SoloStar must be discarded as required by your local authorities.

Maintenance

SoloStar has to be protected from dust and dirt.

The outside of SoloStar can be cleaned by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

SoloStar is designed to work accurately and safely. It should be handled with care. Situations where SoloStar might be damaged must be avoided. If you are concerned that your SoloStar may be damaged, use a new one.

Step 1 Check the Insulin

The label on the pen should be checked to make sure it contains the correct insulin. The Apidra SoloStar is blue. It has a dark blue injection button with a raised ring on the top. After removing the pen cap, the appearance of insulin should also be checked: the insulin solution must be clear, colourless, with no solid particles visible, and must have a water-like consistency.

Step 2 Attach the needle

Only needles that are compatible for use with SoloStar should be used.
A new sterile needle will be always used for each injection. After removing the cap, the needle should be carefully attached straight onto the pen.

Step 3 Perform a safety test

Prior to each injection a safety test has to be performed.
Select a dose of 2.
The outer and inner needle caps should be removed.

While holding the pen with the needle pointing upwards, the insulin reservoir should be tapped gently with the finger so that any air bubbles rise up towards the needle.

Then the injection button should be pressed in completely.
If insulin has been expelled through the needle tip, then the pen and the needle are working properly.
If no insulin appears at the needle tip, step 3 should be repeated until insulin appears at the needle tip.

Step 4 Select the dose

The dose can be set in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If a dose greater than 80 units is required, it should be given as two or more injections.

The dose window must show “0” following the safety test. The dose can then be selected.

Step 5 Inject the dose

The patient should be informed on the injection technique by his health care professional.

The needle should be inserted into the skin.
The injection button should be pressed in completely. Then the injection button should be held down 10 seconds before withdrawing the needle. This ensures that the full dose of insulin has been injected.

Step 6 Remove and discard the needle

The needle should always be removed after each injection and discarded. This helps prevent contamination and/or infection, entry of air into the insulin reservoir and leakage of insulin. Needles must not be reused.
Special caution must be taken when removing and disposing the needle. Follow recommended safety measures for removal and disposal of needles (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

The pen cap should be replaced on the pen.
Mixing with insulins

When mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing, as no data are available regarding the mixtures made up a significant time before injection.

7. MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH, Brueningstrasse 50, D-65926 Frankfurt am Main, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/029-036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 2004

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
Germany

Name and address of the manufacturer(s) responsible for batch release

Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, D-65926 Frankfurt
Germany

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

- **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100 Units/ml, solution for injection in vial
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in vial.
1 vial of 10ml.
2 vials of 10ml.
4 vials of 10ml.
5 vials of 10ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solutions.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Unopened vials
Store in a refrigerator. Do not freeze.
Keep the vial in the outer carton in order to protect from light.

After first use: the product may be stored for a maximum of 4 weeks not above 25°C. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/001 1 vial of 10ml
EU/1/04/285/002 2 vials of 10ml.
EU/1/04/285/003 4 vials of 10ml
EU/1/04/285/004 5 vials of 10ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100Units/ml
Solution for injection in vial
Insulin glulisine.

Subcutaneous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100Units/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
1 cartridge of 3ml.
3 cartridges of 3ml.
4 cartridges of 3ml.
5 cartridges of 3ml.
6 cartridges of 3ml.
8 cartridges of 3ml.
9 cartridges of 3ml.
10 cartridges of 3ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Use only clear and colourless solutions.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: the product may be stored for a maximum of 4 weeks not above 25°C. Do not refrigerate. Keep the cartridge inserted in the pen protected from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/005 1 cartridge of 3ml
EU/1/04/285/006 3 cartridges of 3ml.
EU/1/04/285/007 4 cartridges of 3ml.
EU/1/04/285/008 5 cartridges of 3ml.
EU/1/04/285/009 6 cartridges of 3ml.
EU/1/04/285/010 8 cartridges of 3ml.
EU/1/04/285/011 9 cartridges of 3ml.
EU/1/04/285/012 10 cartridges of 3ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100Units/ml
Solution for injection in cartridge.
Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

This cartridge is for use in conjunction with an insulin pen such as OptiPen.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ALUMINIUM FOIL WHICH IS USED FOR SEALING TRANSPARENT PLASTIC TRAY CONTAINING THE CARTRIDGE

1. NAME OF THE MEDICINAL PRODUCT

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

4. BATCH NUMBER

5. OTHER

After inserting a new cartridge:
You must check that your insulin pen is working properly before you inject the first dose. Consult your insulin pen instruction booklet for further details.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON (cartridge for OptiClik)

1. NAME OF THE MEDICINAL PRODUCT

Apidra 100Units/ml, solution for injection in cartridge.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in cartridge.
1 cartridge of 3ml
3 cartridges of 3ml
4 cartridges of 3ml
5 cartridges of 3ml
6 cartridges of 3ml
8 cartridges of 3ml
9 cartridges of 3ml
10 cartridges of 3ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Use only clear and colourless solutions.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Unopened cartridges:
Store in a refrigerator.
Do not freeze.
Keep the cartridge in the outer carton in order to protect from light.

After first use: the product may be stored for a maximum of 4 weeks not above 25°C.Do not refrigerate. Keep the cartridge inserted in the pen protected from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/021 1 cartridge of 3ml
EU/1/04/285/022 3 cartridges of 3ml
EU/1/04/285/023 4 cartridges of 3ml
EU/1/04/285/024 5 cartridges of 3ml
EU/1/04/285/025 6 cartridges of 3ml
EU/1/04/285/026 8 cartridges of 3ml
EU/1/04/285/027 9 cartridges of 3ml
EU/1/04/285/028 10 cartridges of 3ml

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARTRIDGE LABEL for OptiClik

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra 100Units/ml
Solution for injection in cartridge.
Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

The cartridges for OptiClik are to be used in conjunction with OptiClik only.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON (PRE-FILLED PEN. OptiSet)

1. NAME OF THE MEDICINAL PRODUCT

Apidra , 100Units/ml.
Solution for injection in a pre-filled pen.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen. OptiSet.
1 pen of 3 ml.
3 pens of 3 ml.
4 pens of 3 ml.
5 pens of 3 ml.
6 pens of 3 ml.
8 pens of 3 ml.
9 pens of 3 ml.
10 pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that have been approved for use with OptiSet.

IMPORTANT INFORMATION
Always first attach a new needle before using OptiSet.
Always perform a Safety Test before using OptiSet.
Read the package leaflet fully before using OptiSet for the first time

New information for use:
- Name of the insulin is printed on the pen
- Dosage selector can only be turned in one direction

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Not in-use pens:
Store in a refrigerator.
Do not freeze.
Keep the pre-filled pen in the outer carton in order to protect from light.

After first use: the product may be stored for a maximum of 4 weeks not above 25°C. Keep the pre-filled pen in the outer carton in order to protect from light.
Do not refrigerate.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/013 1 pen of 3 ml.
EU/1/04/285/014 3 pens of 3 ml.
EU/1/04/285/015 4 pens of 3 ml.
EU/1/04/285/016 5 pens of 3 ml.
EU/1/04/285/017 6 pens of 3 ml.
EU/1/04/285/018 8 pens of 3 ml.
EU/1/04/285/019 9 pens of 3 ml.
EU/1/04/285/020 10 pens of 3 ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (OptiSet)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra , 100 Units/ml.
Solution for injection in a pre-filled pen.
Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

OptiSet

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON (PRE-FILLED PEN. SoloStar)

1. NAME OF THE MEDICINAL PRODUCT

Apidra, 100Units/ml.
Solution for injection in a pre-filled pen.
Insulin glulisine.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 100 Units (equivalent to 3.49 mg) insulin glulisine.

3. LIST OF EXCIPIENTS

Also contains:metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection in a pre-filled pen. SoloStar.
1 pen of 3 ml.
3 pens of 3 ml.
4 pens of 3 ml.
5 pens of 3 ml.
6 pens of 3 ml.
8 pens of 3 ml.
9 pens of 3 ml.
10 pens of 3 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Use only clear and colourless solution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use needles that are compatible for use with SoloStar.

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Unopened
Store in a refrigerator (2°C-8°C). Do not freeze. Keep the pre-filled pen in the outer carton in order to protect from light.

After its first use, the product may be stored for a maximum of 4 weeks not above 25°C. Do not refrigerate.
Keep the pen protected from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi-Aventis Deutschland GmbH
D-65926 Frankfurt am Main, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/285/029 1 pen of 3 ml.
EU/1/04/285/0303 pens of 3 ml.
EU/1/04/285/031 4 pens of 3 ml.
EU/1/04/285/0325 pens of 3 ml.
EU/1/04/285/033 6 pens of 3 ml.
EU/1/04/285/034 8 pens of 3 ml.
EU/1/04/285/035 9 pens of 3 ml.
EU/1/04/285/036 10 pens of 3 ml.

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Apidra

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PEN LABEL (SoloStar)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Apidra, 100Units/ml.
Solution for injection in a pre-filled pen.
Insulin glulisine

Subcutaneous use.

2. METHOD OF ADMINISTRATION

SoloStar

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET:INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in vial
(insulin glulisine)

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if
- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.

Take special care with Apidra

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents.

Taking/using other medicines

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensin converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g. asprin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline] or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take beta-blockers, clonidine or lithium salts or drink alcohol. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (e.g. clonidine, guanethidine, and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:
- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

3. HOW TO USE APIDRA

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Your doctor will determine how much Apidra you will need based on your life-style and the results of blood sugar (glucose) tests and your previous insulin usage.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long -acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle the vials

Look at the vial before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.

Apidra vials are for use with insulin syringes with the corresponding unit scale and for use with an insulin pump system.

If you have to mix two types of insulin

Apidra must not be mixed with any preparation other than NPH human insulin.

If Apidra is mixed with NPH human insulin, Apidra should be drawn into the syringe first. Injection should be given immediately after mixing.

How to handle an infusion pump system

Apidra must never be mixed with diluents or any other insulin when used in a pump.

Before use of Apidra in the pump system you should have received comprehensive instructions of this use. In addition, information about any action to be taken in case of illness, too high or too low blood sugar or failure of the pump system.

Use the type of pump system recommended by your doctor. Read and follow the instructions that accompany your insulin infusion pump. Follow your doctor’s instructions about the basal infusion rate and the mealtime insulin boluses to be taken. To get the benefit of insulin infusion, and to detect possible malfunction of the insulin pump, you should measure your blood sugar level regularly.

The infusion set and reservoir should be changed every 48 hours using aseptic technique.

What to do in case of pump system failure?

You should always have alternative insulin available for injection under the skin in case of pump system failure.

If you take more Apidra than you should

If you **have injected too much Apidra**, your blood sugar may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further recommendations on hyperglycaemia.
Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

A very common (experienced in more than 1 in 10 patients) reported side effect is **hypoglycaemia (low blood sugar) this means that there is not enough sugar in the blood.**If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Common (experienced in more than 1 in 100 but less than 1 in 10 patients) reported side effects are **skin and allergic reactions.** Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon (experienced in more than 1 in 1,000 but less than 1 in 100 patients) side effects reported are systemic allergy. Less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

A rare (experienced in more than 1 in 10,000 but less than 1 in 1,000 patients) side effect may occur if you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.

Other side effects

Hyperglycaemia (high blood sugar) this means that there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Tell your doctor or pharmacist if you notice any of the side effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too <u>high</u> (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high:
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too <u>low</u> (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low blood sugar levels) are also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of

speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g. bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.
Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the label and on the carton. The expiry date refers to the last day of that month.

Unopened
Store in a refrigerator (2°C – 8°C),
Do not freeze.
Ensure that the vial is not directly touching the freezer compartment or freezer packs.

In use conditions:

Once in use, itmay be stored for a maximum of 4 weeks not above 25°C and it is recommended that the date of first use from the vial be noted on the label.
Keep the vial in the outer carton in order to protect from light.
Do not use Apidra if it does not appear clear and colourless.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. One millilitre of the solution contains 100 Units of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml solution for injection in vial is a clear, colourless solution with no particles visible.
Each vial contains 10 ml solution (1000 Units). Packs of 1, 2, 4 and 5 vials of 10 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer:
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This leaflet was last approved on {date}

PACKAGE LEAFLET:INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in cartridge
(insulin glulisine)

Before you start using this medicine please read carefully all of this leaflet and the instructions for using the pen provided with your insulin pen.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if
- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.

Take special care with Apidra

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents.

Taking/using other medicines

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Please tell your doctor or pharmacist if you are taking or have taken recently any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensine converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for the treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g. aspirin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline] or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take beta-blockers, clonidine or lithium salts or drink alcohol. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (e.g. clonidine, guanethidine, and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:
- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

3. HOW TO USE APIDRA

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Your doctor will determine how much Apidra you will need based on your life-style and the results of blood sugar (glucose) tests and your previous insulin usage.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle the cartridge

Look at the cartridge before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.

The cartridges are to be used in conjunction with an insulin pen such as OptiPen as recommended in the information provided by the device manufacturer.

The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection
Before insertion of the cartridge into the reusable pen OptiPen, the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen). Empty cartridges must not be refilled.

Never use OptiPen if it is damaged or if you are not sure that it is working properly.

To prevent any kind of contamination, the reusable pen should be used only by you.

If the pen malfunctions, the solution may be drawn from the cartridge into a syringe (suitable for an insulin with 100 Units/ml) and injected.

If you take more Apidra than you should

If you **have injected too much Apidra**,your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further recommendations on hyperglycaemia.
Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

A very common (experienced in more than 1 in 10 patients) reported side effect is **hypoglycaemia (low blood sugars) this means that there is not enough sugar in the blood**

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Common (experienced in more than 1 in 100 but less than 1 in 10 patients) reported side effects are **skin and allergic reactions.** Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon (experienced in more than 1 in 1,000 but less than 1 in 100 patients) side effects reported are systemic allergy. Less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

A rare (experienced in more than 1 in 10,000 but less than 1 in 1,000 patients) side effect may occur if you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.

Other side effects
Hyperglycaemia (high blood sugars) this means that there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Tell your doctor or pharmacist if you notice any of the side effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too high (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too low (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low blood sugar levels) are also more likely to occur if :
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g. bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.

Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the label and carton. The expiry date refers to the last day of that month.

Unopened
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:

Once in use, it may be stored for a maximum of 4 weeks not above 25°C. Do not refrigerate.

Keep the cartridge inserted in the pen protected from light.

Do not use Apidra if it does not appear clear and colourless.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. One millilitre of the solution contains 100 Units of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml solution for injection in cartridge is a clear, colourless solution with no particles visible.
Each cartridge contains 3 ml solution (300 Units). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer:
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PACKAGE LEAFLET:INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in cartridge for OptiClik
(insulin glulisine)

Read all of this leaflet carefully before you start using this medicine. The instructions for using OptiClik, the insulin pen, are provided with your OptiClik. Please refer to them before using your medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if
- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.

Take special care with Apidra

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents.

Taking/using other medicines

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Please tell your doctor or pharmacist if you are taking or have taken recentlyany other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensine converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for the treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g. aspirin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline] or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take beta-blockers, clonidine or lithium salts or drink alcohol. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (e.g. clonidine, guanethidine, and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:
- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

3. HOW TO USE APIDRA

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Your doctor will determine how much Apidra you will need based on your life-style and the results of blood sugar (glucose) tests and your previous insulin usage.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle the cartridge for OptiClik

Look at the cartridge before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.
Apidra in cartridge for OptiClik has been developed for use in OptiClik only**.** The manufacturer's instructions for using the pen must be followed carefully for loading the cartridge, attaching the needle, and administering the insulin injection

Before insertion of the cartridge into the reusable pen OptiClik the cartridge must be stored at room temperature for 1 to 2 hours. Air bubbles must be removed from the cartridge before injection (see instruction for using pen). Empty cartridges must not be refilled.

Problems with OptiClik?

Please refer to the manufacturer's instructions for using the pen.
If OptiClik is damaged or not working properly (due to mechanical defects) it has to be discarded, and a new OptiClik has to be used.

To prevent any kind of contamination, the reusable pen should be used only by you.

If the OptiClik does not function well, you can draw the insulin from the cartridge into a syringe for injection. Therefore, keep syringes and needles as well. However, use only syringes which are designed for an insulin concentration of 100 Units per millilitre.

If you take more Apidra than you should

If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further recommendations on hyperglycaemia.
Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

A very common (experienced in more than 1 in 10 patients) reported side effect is **hypoglycaemia (low blood sugars) this means that there is not enough sugar in the blood.**

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Common (experienced in more than 1 in 100 but less than 1 in 10 patients) reported side effects are **skin and allergic reactions.** Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon (experienced in more than 1 in 1,000 but less than 1 in 100 patients) side effects reported are systemic allergy. Less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

A rare (experienced in more than 1 in 10,000 but less than 1 in 1,000 patients) side effect may occur if you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.

Other side effects

Hyperglycaemia (high blood sugars) this means that there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Tell your doctor or pharmacist if you notice any of the side effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too high (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too low (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low blood sugar levels) are also more likely to occur if :
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g.bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.

Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the label and carton. The expiry date refers to the last day of that month.

Unopened
Store in a refrigerator (2°C – 8°C).
Do not freeze.
Ensure that the container is not directly touching the freezer compartment or freezer packs.

In use conditions:

Once in use, it may be stored for a maximum of 4 weeks not above 25°C. Do not refrigerate.

Keep the cartridge inserted in the pen protected from light.

Do not use Apidra if it does not appear clear and colourless.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. One millilitre of the solution contains 100 Units of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml solution for injection in cartridge is a clear, colourless solution with no particles visible. **This cartridge is for use with OptiClik only.**
Each cartridge contains 3 ml solution (300 Units). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 cartridges of 3 ml are available. Not all pack sizes may be marketed.

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This leaflet was last approved on {date}

PACKAGE LEAFLET:INFORMATION FOR THE USER
Apidra 100 Units/ml solution for injection in a pre-filled pen.
(insulin glulisine)

Read carefully all of this leaflet including the Instructions for Use of Apidra (pre-filled pen, OptiSet) before using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you ;Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if
- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.

Take special care with Apidra

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents.

Taking/using other medicines

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensin converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for the treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g.aspirin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline]or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

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If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:
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- reduced or absent warning signs of hypoglycaemia.

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Apidra should be taken shortly (0-15 minutes) before or soon after meals.

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Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle OptiSet

OptiSet is a pre-filled disposable pen containing insulin glulisine.

Read carefully the "OptiSet Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Before use always attach a new needle, and perform a safety test. Only use needles that have been approved for use with OptiSet.

Look at the cartridge sealed in the disposable pen injector before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with OptiSet, please refer to the Questions and Answers section of the attached OptiSet Instructions for Use, or have it checked by your doctor or pharmacist.

If you take more Apidra than you should

If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further information on hyperglycaemia.
Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.
A very common (experienced in more than 1 in 10 patients) reported side effect is **hypoglycaemia (low blood sugars) this means that there is not enough sugar in the blood.**

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Common (experienced in more than 1 in 100 but less than 1 in 10 patients) reported side effects are **skin and allergic reactions.** Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon (experienced in more than 1 in 1,000 but less than 1 in 100 patients) side effects reported are systemic allergy. Less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

A rare (experienced in more than 1 in 10,000 but less than 1 in 1,000 patients) side effect may occur if you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.
Other side effects

Hyperglycaemia (high blood sugars) this means there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Tell your doctor or pharmacist if you notice any of the side effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too high (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too low (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low blood sugar levels) are also more likely to occur if :
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g.bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.
Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the label and carton. The expiry date refers to the last day of that month.

<u>Unopened</u>
Store in a refrigerator (2°C - 8°C).
Keep the pre-filled pen in the outer carton in order to protect from light.
Do not freeze.
Ensure that the pre-filled pen is not directly touching the freezer compartment or freezer packs.

In use conditions
Once in use, it may be stored for a maximum of 4 weeks not above 25°C. Do not refrigerate.
Keep the pre-filled pen in the outer carton in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
Do not use Apidra if it does not appear clear and colourless.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. One millilitre of the solution contains 100 Units of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml, solution for injection in a pre-filled pen. OptiSet. is a clear, colourless solution with no particles visible.
Each pen contains 3 ml solution (300 Units). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pre-filled pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer:
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

OPTISET INSTRUCTIONS FOR USE

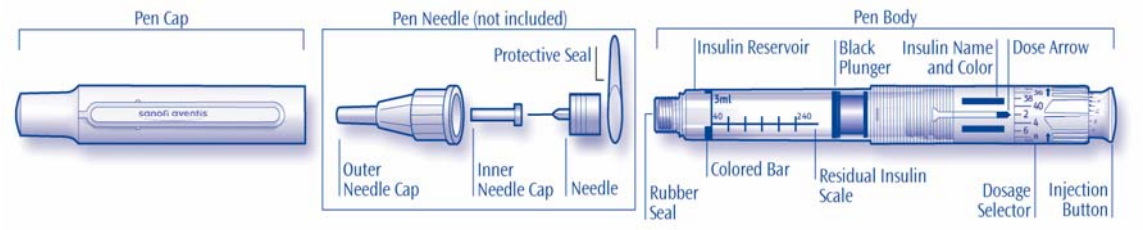
OptiSet is a disposable pen for the injection of insulin. Doses from 2 to 40 units can be set in steps of 2 units.

Talk with your healthcare professional about proper injection technique before using OptiSet.

Read these instructions carefully before using your OptiSet. If you are not able to follow all the instructions completely on your own, use OptiSet only if you have help from a person who is able to follow the instructions.

If you have any questions about OptiSet or about diabetes, ask your healthcare professional or call the local sanofi-aventis number on the front of this leaflet.

Keep this leaflet for future reference each time you use OptiSet.



New information for use:

- Name of the insulin is printed on the pen
- Dosage selector can only be turned in one direction

Important information for use of OptiSet:

- Always attach a new needle before each use. Only use needles that are compatible for use with OptiSet.
- Always perform the safety test before each injection.
- If you are using a new OptiSet the initial safety test must be done with the 8 units preset by the manufacturer.
- The dosage selector can only be turned in one direction.
- Never turn the dosage selector (i.e. never change the dose) after injection button has been pulled out.
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use OptiSet if it is damaged or if you are not sure that it is working properly.
- Always have a spare OptiSet in case your OptiSet is lost or damaged.

Step 1. Check the insulin

A. Take off the pen cap.

B. Check the label on the pen and insulin reservoir to make sure you have the correct insulin.

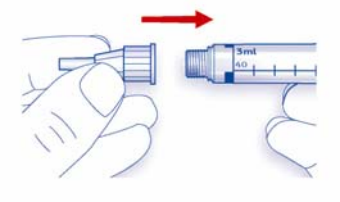
C. Apidra is a clear insulin. Do not use this OptiSet if the insulin is cloudy, coloured or has particles.

Step 2. Attach the needle

Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or the needle can be bent.

Step 3. Perform a safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:

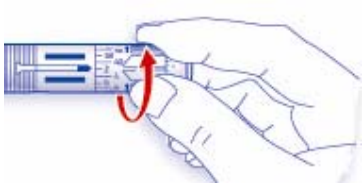
- making sure that pen and needle work properly
- removing air bubbles

If you are using a new OptiSet the initial safety test must be done with the 8 units preset by the manufacturer, otherwise the pen will not function properly.

A. Make sure the injection button is pressed in.

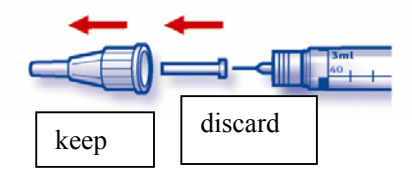
B. Select the dose for the Safety Test.

- New and unused OptiSet: a dose of 8 units is already preset by the manufacturer for the first safety test.
- In-use OptiSet: select a dose of 2 units by turning the dosage selector forward till the dose arrow points to 2. The dosage selector will only turn in one direction.



C. Pull out the injection button completely in order to load the dose. Never turn the dosage selector after injection button has been pulled out.

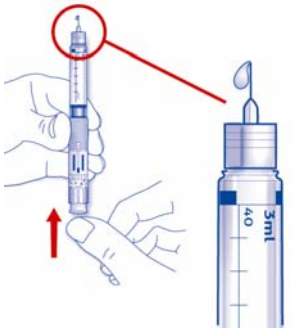
D. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



E. Hold the pen with the needle pointing upwards.

F. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

G. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

- If no insulin comes out, check for air bubbles and repeat the safety test two more times.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your OptiSet may be damaged. Do not use this OptiSet.

Step 4. Select the dose

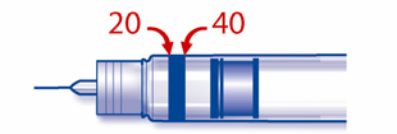
You can set the dose in steps of 2 units, from a minimum of 2 units to a maximum of 40 units. If you need a dose greater than 40 units, you should give it as two or more injections.

A. Check if you have enough insulin for your dose.

- The residual insulin scale on the transparent insulin reservoir shows approximately how much insulin remains in the OptiSet. This scale must not be used to set the insulin dose.

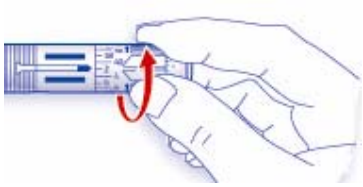
- If the black plunger is at the beginning of the coloured bar, then there are approximately 40 units of insulin available.

- If the black plunger is at the end of the coloured bar, then there are approximately 20 units of insulin available.



B. Select your required dose by turning the dose selector forward.
If you turned past your dose,

- and you have not yet pulled the injection button, you can keep turning forward till you reach your dose again,
- and you have already pulled the injection button out, you must discard the dose that has been loaded **before** you turn the dosage selector again.



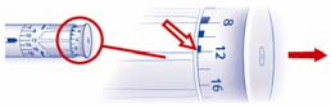
Step 5. Load the dose

A. Pull out the injection button completely in order to load the dose.

B. Check if the selected dose is fully loaded. Note that the injection button only goes out as far as the amount of insulin that is left in the reservoir.

- The injection button must be held out under tension during this check.
- The last thick line visible on the injection button shows the amount of insulin loaded. When the injection button is held out only the top part of this thick line can be seen.
- In this example, 12 units are loaded.

    - o if you have selected 12 units you can inject your dose.
    - o if you have selected more than 12 units then only 12 units of your total insulin dose can be injected with this pen.



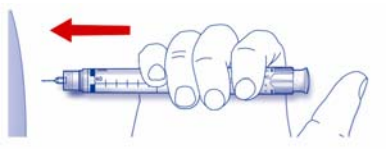
In this case what should you do:

- either you can inject what is remaining in the pen and complete your dose with a new OptiSet.
- or use a new OptiSet for your full dose..

Step 6. Inject the dose

A. Use the injection method as instructed by your health care professional.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. A clicking sound can be heard, which will stop when the injection button has been pressed in completely.

D. Keep the injection button pressed in and slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

Step 7. Remove and discard the needle

Always remove the needle after each injection and store OptiSet without a needle attached. This helps prevent:

- Contamination and/or infection
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, special caution must be taken by this person when removing and disposing the needle. Follow recommended safety measures for removal and disposal of needles (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely, as instructed by your healthcare professional.

C. Put the pen cap back on, then store the pen until your next injection.

Storage Instructions

Please check Section 5 - How to store Apidra- of the reverse (insulin) side of this leaflet for OptiSet storage instructions.

If your OptiSet is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up to room temperature. Cold insulin is more painful to inject.

Discard your used OptiSet as required by your local regulations.

Maintenance

Protect your Optiset from dust and dirt.

You can clean the outside of your OptiSet by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your OptiSet is designed to work accurately and safely. It should be handled with care. Avoid situations where OptiSet might be damaged. If you are concerned that your OptiSet may be damaged, discard it and use a new one.

Questions and Answers

Wrong dose selected.	• Follow the instructions in Step 4 to select the correct dose.
Dose has been selected and the injection button has been pulled out and pressed in again without a needle attached.	1. Attach a new needle. 2. Press the injection button completely in and discard the insulin. 3. Perform the safety test. If the safety test is successful OptiSet is ready for use. If test is not successful, the pen might be damaged. Use a new OptiSet. If in any doubt whether the pen is working correctly use a new OptiSet.
The dosage selector does not turn.	• You are turning in the wrong direction. The dosage selector can only be turned forward. • You are turning forward while the injection button is pulled out. Press the injection button in completely to discard the dose and select again.
The amount indicated on the injection button is higher than the dose selected.	• Difference is 2 units. Discard insulin, then set your dose and check again. If the same error occurs again, OptiSet may be damaged, use a new OptiSet. • Difference is more than 2 units OptiSet is damaged, use a new OptiSet.
The amount indicated on the injection button is lower than the dose selected	There is not enough insulin in the reservoir • you can inject the amount indicated on the injection button from this OptiSet and then inject the remaining dose using a new pen, or • you can inject the entire dose using a new pen.
The injection button cannot be pressed in.	1. Make sure you pulled out the injection button completely. 2. Attach a new needle. 3. Press the injection button completely in to discard the insulin. 4. Perform the safety test.
You don't hear clicking while injecting.	OptiSet is damaged, use a new OptiSet.

Insulin is leaking from the pen.	Needle may have been attached imprecisely (e.g. at a slant). Remove needle and replace with a new needle attaching it on straight. Perform the safety test.
Air bubbles are present in the reservoir.	Small amounts of air may be present in the needle and insulin reservoir during normal use. You must remove this air by performing the safety test. The tiny air bubbles in the insulin reservoir that do not move with tapping will not interfere with the injection and dosage.
OptiSet is damaged or is not working properly.	Do not force it. Do not try to repair nor use tools on it. Use a new OptiSet.
OptiSet has been dropped or subjected to impact.	If in any doubt whether the pen is working correctly use a new OptiSet.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Apidra 100 Units/ml solution for injection in a pre-filled pen.
(insulin glulisine)

Read carefully all of this leaflet including the Instructions for Use of Apidra (pre-filled pen, SoloStar) before using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT APIDRA IS AND WHAT IT IS USED FOR

Apidra is a clear, colourless, aqueous solution for injection containing insulin glulisine. Insulin glulisine is produced by recombinant DNA technology in *Escherichia coli* microorganism. Insulin glulisine has a rapid onset of action and a short duration of action.

Apidra is an antidiabetic agent, used to reduce high blood sugar in patients with diabetes mellitus. Diabetes mellitus is a disease where your body does not produce enough insulin to control the level of blood sugar.

2. BEFORE YOU USE APIDRA

Do not use Apidra if
- Your blood sugar is too low (hypoglycaemia). Follow the guidance for hypoglycaemia.
- You are allergic (hypersensitive) to insulin glulisine or any of the other ingredients of Apidra.

Take special care with Apidra

Please follow closely the instructions for dosage, monitoring (blood tests), diet and physical activity (physical work and exercise) as discussed with your doctor.

Special patient groups

Impairment of your liver or kidney may reduce your insulin requirements.

There is no adequate clinical information on the use of Apidra in children and adolescents.

Taking/using other medicines

Some medicines cause the blood sugar level to fall, some cause it to rise, others may have both effects, depending on the situation. In each case, it may be necessary to adjust your insulin dosage to avoid too low or too high blood sugar levels. Be careful not only when you start another medicine, but also when you stop it.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Before taking a medicine ask your doctor if it can affect your blood sugar level and what action, if any, you need to take.

Medicines that may cause your blood sugar to fall include all other medicines for the treatment of diabetes, angiotensin converting enzyme (ACE) inhibitors (used for the treatment of certain heart conditions, high blood pressure or elevated protein/albumin in the urine), disopyramide (used for the treatment of certain heart conditions), fluoxetine (used for the treatment of depression), fibrates (used to lower abnormally high blood levels of blood lipids), monoamine oxidase (MAO) inhibitors (used for the treatment of depression), pentoxifylline, propoxyphene, salicylates (e.g.aspirin, used to relieve pain and lower fever) and sulfonamide antibiotics.

Medicines that may cause your blood sugar to rise include corticosteroids ("cortisone"), danazol, diazoxide, diuretics, glucagon, isoniazid, oestrogens and progestogens (e.g. in the contraceptive pill used for birth control), phenothiazine derivatives, somatropin, sympathomimetic medicines (e.g. epinephrine [adrenaline] or salbutamol, terbutaline used for the treatment of asthma), thyroid hormones (used for the treatment of malfunction of the thyroid gland), protease inhibitors and atypical antipsychotic medications (e.g; olanzapine and clozapine).

Your blood sugar level may either rise or fall if you take beta-blockers, clonidine or lithium salts or drink alcohol. Pentamidine may cause hypoglycaemia which may sometimes be followed by hyperglycaemia.

Beta-blockers like other sympatholytic medicines (e.g. clonidine, guanethidine, and reserpine) may weaken the warning symptoms of a hypoglycaemic reaction or suppress them entirely.

If you are not sure whether you are taking one of those medicines ask your doctor or pharmacist.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Inform your doctor if you are planning to become pregnant, or if you are already pregnant. Your insulin dosage may need to be changed during pregnancy and after giving birth. Careful control of your diabetes, and prevention of hypoglycaemia, is important for the health of your baby.

There are no adequate data on the use of Apidra in pregnant women.

If you are breast-feeding consult your doctor as you may require adjustments in your insulin doses and your diet.

Driving and using machines

Your ability to concentrate or react may be reduced if you have too low (hypoglycaemia) or too high (hyperglycaemia) blood sugar. Please keep this possible problem in mind in all situations where you might put yourself and others at risk (e.g. driving a car or operating machinery). You should contact your doctor for advice on driving if you have:
- frequent episodes of hypoglycaemia,
- reduced or absent warning signs of hypoglycaemia.

3. HOW TO USE APIDRA

Apidra should be taken shortly (0-15 minutes) before or soon after meals.

Your doctor will determine how much Apidra you will need based on your life-style and the results of blood sugar (glucose) tests and your previous insulin usage.

Apidra is a short-acting insulin. Your doctor may tell you to use it in combination with an intermediate or long acting insulin or a basal insulin or with tablets against high blood sugar.

If you switch from another insulin to insulin glulisine, your dosage may have to be adjusted by your doctor.

Many factors may influence your blood sugar level. You should know these factors to be able to react correctly to changes in your blood sugar level and to prevent it from becoming too high or too low. See the box at the end of section 4 for further information.

Apidra is injected under the skin (subcutaneously).

Your doctor will advise you in which area of the skin you should inject Apidra. Apidra can be injected in the abdominal wall, the thigh or upper arm or by continuous infusion in the abdominal wall. You will feel the effect slightly more quickly if the insulin is injected into your abdomen. As for all insulins, injection sites and infusion sites within an-injection area (abdomen, thigh or upper arm) must be rotated from one injection to the next.

How to handle SoloStar

SoloStar is a pre-filled disposable pen containing insulin glulisine.

Read carefully the " SoloStar Instructions for Use" included in this package leaflet. You must use the pen as described in these Instructions for Use.

To prevent the possible transmission of disease, each pen must be used by one patient only.

Before use always attach a new needle, and perform a safety test. Only use needles that are compatible for use with SoloStar (see “SoloStar Instructions for Use”).

Look at the cartridge sealed in the disposable pen injector before you use it. Only use it if the solution is clear, colourless and has no visible particles in it. Apidra is a solution and does not require shaking or mixing before use.

Always use a new pen if you notice that your blood sugar control is unexpectedly getting worse. If you think you may have a problem with SoloStar, please consult your Health Care Professional.

If you take more Apidra than you should

If you **have injected too much Apidra**, your blood sugar level may become too low (hypoglycaemia). Check your blood sugar frequently. In general, to prevent hypoglycaemia you must eat more food and monitor your blood sugar. For information on the treatment of hypoglycaemia, see reference box at the end of section 4.

If you forget to take Apidra

If you **have missed a dose of Apidra** or if you **have injected too low a dose,** your blood sugar level may become too high (hyperglycaemia). Check your blood sugar frequently. See carefully reference box at the end of section 4 for further information on hyperglycaemia.
Do not take a double dose to make up for a forgotten dose.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Apidra can cause side effects, although not everybody gets them.

A very common (experienced in more than 1 in 10 patients) reported side effect is **hypoglycaemia (low blood sugars) this means that there is not enough sugar in the blood.**

If your blood sugar level falls too much you may become unconscious. Serious hypoglycaemia may cause brain damage and may be life-threatening. You should be able to recognise when your blood sugar is falling too much, so that you can take the correct actions. Please see the box at the end of this section for important further information about hypoglycaemia and its treatment.

Common (experienced in more than 1 in 100 but less than 1 in 10 patients) reported side effects are **skin and allergic reactions.** Reactions at the injection site may occur (e.g. reddening, unusually intense pain on injection, itching, hives, swelling or inflammation). They can also spread around the injection site. Most minor reactions to insulins usually resolve in a few days to a few weeks.

Uncommon (experienced in more than 1 in 1,000 but less than 1 in 100 patients) side effects reported are systemic allergy. Less common but potentially more serious, is a generalised allergy to insulin which may cause rash (including pruritus) over the whole body, shortness of breath, wheezing, reduction of blood pressure, rapid pulse, or sweating. Severe cases of generalised reactions, including anaphylactic reaction, may be life-threatening.

A rare (experienced in more than 1 in 10,000 but less than 1 in 1,000 patients) side effect may occur if you inject your insulin too often at the same skin site, fatty tissue under the skin at this site may shrink or thicken (called lipodystrophy). Insulin that you inject in such a site may not work very well. Changing the site with each injection may help to prevent such skin changes.

Other side effects

Hyperglycaemia (high blood sugars) this means there is too much sugar in the blood

If your blood sugar level is too high, this tells you that you could have needed more insulin than you injected. Please see the box at the end of this section for further information.

Eye reactions

A marked change (improvement or worsening) in your blood sugar control can cause a temporary worsening of your vision. If you have proliferative retinopathy (an eye disease related to diabetes) severe hypoglycaemic attacks may cause transient loss of vision.

Tell your doctor or pharmacist if you notice any of the side effects listed above or any other unwanted or unexpected effects. To prevent serious reactions, speak to a doctor immediately if a side effect is severe, occurs suddenly or gets rapidly worse.

If your blood sugar is too high (hyperglycaemia)

Your blood sugar level may be too high if, for example:
- you have not injected your insulin or not injected enough, or if it has become less effective, e.g. through incorrect storage,
- you are doing less physical exercise, you are under stress (emotional distress, excitement), or if you have an injury, operation, feverish illness or certain other diseases,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines").

Symptoms that may tell you that your blood sugar levels are too high
Thirst, increased need to urinate, tiredness, dry skin, reddening of the face, loss of appetite, low blood pressure, fast heart beat, elevated blood glucose levels and ketone bodies and/or glucose in the urine. Stomach pain, fast and deep breathing, sleepiness or even loss of consciousness may be signs of a serious condition (ketoacidosis) resulting from lack of insulin.

Test your blood sugar level and your urine for ketones as soon as any such symptoms of hyperglycaemia occur as described above. Severe hyperglycaemia or ketoacidosis must always be treated by a doctor, normally in a hospital.

If your blood sugar is too low (hypoglycaemia)

Your blood sugar levels may fall too much if, for example:
- you inject too much insulin,
- you miss meals or delay them,
- you do not eat enough, or eat food containing less carbohydrate than normal (sugar and substances similar to sugar are called carbohydrates; however, artificial sweeteners are NOT carbohydrates),
- you lose carbohydrates due to vomiting or diarrhoea,
- you drink alcohol, particularly if you are not eating much,
- you take more physical exercise than usual or a different type of physical activity,
- you are recovering from an injury or operation or other stress,
- you are recovering from a feverish illness or from another illness,
- you are taking or have stopped taking certain other medicines (see section 2, "Taking/using other medicines").

Hypoglycaemia (low bllod sugar levels) are also more likely to occur if:
- you have just begun insulin treatment or changed to another insulin preparation,
- your blood sugar levels are almost normal or are unstable,
- you change the area of skin where you inject insulin (e.g. from the thigh to the upper arm),
- you suffer from severe kidney or liver disease, or some other disease such as hypothyroidism.

Symptoms that tell you that your blood sugar level is falling too much or too fast may be, for example: sweating, clammy skin, anxiety, fast heart beat, high blood pressure, palpitations and irregular heartbeat. These symptoms often develop before the symptoms of a low sugar level in the brain.

The following symptoms indicate a low sugar level in the brain: headaches, intense hunger, nausea, vomiting, tiredness, sleepiness, sleep disturbances, restlessness, aggressive behaviour, lapses in concentration, impaired reactions, depression, confusion, speech disturbances (sometimes total loss of speech), visual disorders, trembling, paralysis, tingling sensations (paraesthesia), numbness and tingling sensations in the area of the mouth, dizziness, loss of self-control, inability to look after yourself, convulsions and loss of consciousness.

The first symptoms which alert you to hypoglycaemia ("warning symptoms") may change, be less obvious or may be more possibly missing altogether if:
- you are elderly,
- you have had diabetes for a long time,
- you, due to diabetes, suffer from a certain type of nervous disease (autonomic neuropathy),
- you have recently suffered hypoglycaemia (e.g. the day before) or if it develops slowly,
- you have almost normal or, at least, greatly improved blood sugar levels,
- you are taking or have taken certain other medicines (see section 2, "Taking/using other medicines.)

In such a case, you may develop severe hypoglycaemia (and even lose consciousness) before you are aware of the problem. Try always to keep familiar with your warning symptoms. If necessary, more frequent blood sugar testing can help to identify mild hypoglycaemic episodes that might otherwise be overlooked. While you are not confident about recognising your warning symptoms, avoid situations (e.g. driving a car) in which you or others would be put at risk by hypoglycaemia.

What to do in case of hypoglycaemia?

1. Do not inject insulin. Immediately take about 10 to 20 g sugar, e.g. glucose, sugar cubes or a sugar-sweetened beverage. (Measure once as spoonfuls or lumps of sugar or glucose tablets to see how much this means.) Caution: please remember that artificial sweeteners and foods with artificial sweeteners (e.g. diet drinks) are of no help in hypoglycaemia.
2. Then eat something that has a long-acting effect in raising your blood sugar (e.g.bread). Your doctor or nurse will have discussed this with you.
3. If the hypoglycaemia comes back again take another 10 to 20 g sugar.
4. Speak to a doctor immediately if you are not able to control the hypoglycaemia or if it recurs.

Always carry some sugar (at least 20 grams) with you.
Tell people in your environment the following: If you are not able to swallow or if you are unconscious, you will require an injection of glucose or glucagon (a medicine which increases blood sugar). These injections are justified even if it is not certain that you have hypoglycaemia.

It is advisable to test your blood sugar immediately after taking glucose to check that you really have hypoglycaemia.

Carry some information with you to show you are diabetic.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE APIDRA

Keep out of the reach and sight of children.
Do not use Apidra after the expiry date, which is stated on the carton and on the label. The expiry date refers to the last day of that month.

Unopened
Store in a refrigerator (2°C-8°C). Keep the pre-filled pen in the outer carton in order to protect from light. Do not allow it to freeze. Do not put SoloStar next to the freezer compartment of your refrigerator or next to a freezer pack.

Before first use, keep a new pen at room temperature for 1 or 2 hours.

In use conditions

If the pen has been taken out of cool storage, either for use or to be carried as a spare, you can use it for up to 4 weeks. During this time, it can be safely kept at room temperature up to 25°C protected from light and it must not be stored in the refrigerator. Do not use it after this time.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Apidra contains

- The active substance is insulin glulisine. One millilitre of the solution contains 100 Units of the active substance insulin glulisine (equivalent to 3.49 mg).
- The other ingredients are: metacresol, sodium chloride, trometamol, polysorbate 20, concentrated hydrochloric acid, sodium hydroxide, water for injections

What Apidra looks like and contents of the pack

Apidra 100 Units/ml, solution for injection in a pre-filled pen. SoloStar. is a clear, colourless solution with no particles visible.

Each pen contains 3 ml solution (300 Units). Packs of 1, 3, 4, 5, 6, 8, 9 and 10 pre-filled pens of 3 ml are available. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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The manufacturer is:
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This leaflet was last approved on {date}

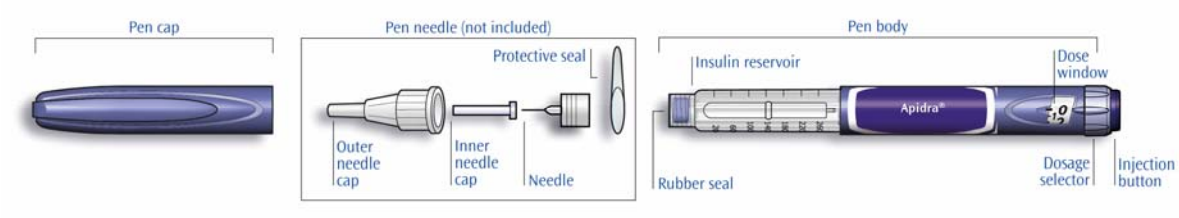
Apidra solution for injection in a pre-filled pen. SoloStar. INSTRUCTIONS FOR USE

Your healthcare professional has decided that SoloStar is right for you. Talk with your healthcare professional about proper injection technique before using SoloStar.

Read these instructions carefully before using your SoloStar. If you are not able to follow all the instructions completely on your own, use SoloStar only if you have help from a person who is able to follow the instructions.

SoloStar is a disposable pen for the injection of insulin. You can set doses from 1 to 80 units in steps of 1 unit.

Keep this leaflet for future reference.



Schematic diagram of the pen

Important information for use of SoloStar:

- Always attach a new needle before each use. Only use needles that are compatible for use with SoloStar.
- Always perform the safety test before each injection.
- This pen is only for your use. Do not share it with anyone else.
- If your injection is given by another person, special caution must be taken by this person to avoid accidental needle injury and transmission of infection.
- Never use SoloStar if it is damaged or if you are not sure that it is working properly.
- Always have a spare SoloStar in case your SoloStar is lost or damaged.

Step 1. Check the insulin

A. Check the label on your SoloStar to make sure you have the correct insulin. The Apidra Solostar is blue. It has a dark blue injection button with a raised ring on the top.

B. Take off the pen cap.

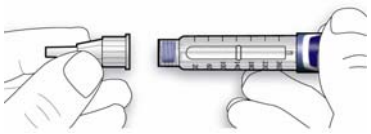
C. Check the appearance of your insulin. Apidra is a clear insulin. Do not use this SoloStar if the insulin is cloudy, coloured or has particles.

Step 2. Attach the needle

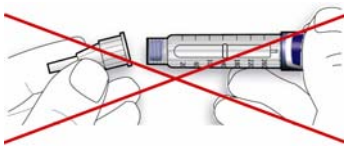
Always use a new sterile needle for each injection. This helps prevent contamination, and potential needle blocks.

A. Remove the protective seal from a new needle.

B. Line up the needle with the pen, and keep it straight as you attach it (screw or push on, depending on the needle type).



- If the needle is not kept straight while you attach it, it can damage the rubber seal and cause leakage, or break the needle.



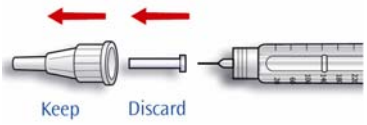
Step 3. Perform a Safety test

Always perform the safety test before each injection. This ensures that you get an accurate dose by:

- ensuring that pen and needle work properly
- removing air bubbles

A. Select a dose of 2 units by turning the dosage selector.

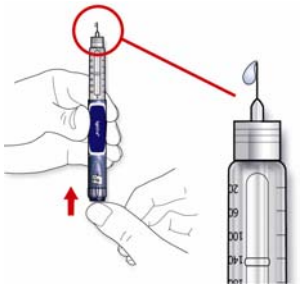
B. Take off the outer needle cap and keep it to remove the used needle after injection. Take off the inner needle cap and discard it.



C. Hold the pen with the needle pointing upwards.

D. Tap the insulin reservoir so that any air bubbles rise up towards the needle.

E. Press the injection button all the way in. Check if insulin comes out of the needle tip.



You may have to perform the safety test several times before insulin is seen.

- If no insulin comes out, check for air bubbles and repeat the safety test two more times to remove them.
- If still no insulin comes out, the needle may be blocked. Change the needle and try again.
- If no insulin comes out after changing the needle, your SoloStar may be damaged. Do not use this SoloStar.

Step 4. Select the dose

You can set the dose in steps of 1 unit, from a minimum of 1 unit to a maximum of 80 units. If you need a dose greater than 80 units, you should give it as two or more injections.

A. Check that the dose window shows "0" following the safety test.

B. Select your required dose (in the example below, the selected dose is 30 units). If you turn past your dose, you can turn back down.

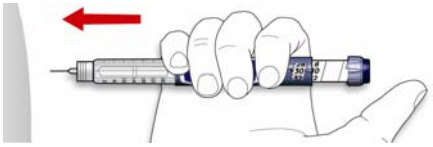
- Do not push the injection button while turning, as insulin will come out.

- You cannot turn the dosage selector past the number of units left in the pen. Do not force the dosage selector to turn. In this case, either you can inject what is remaining in the pen and complete your dose with a new SoloStar or use a new SoloStar for your full dose.

Step 5. Inject the dose

A. Use the injection method as instructed by your healthcare professional.

B. Insert the needle into the skin.



C. Deliver the dose by pressing the injection button in all the way. The number in the dose window will return to "0" as you inject.

D. Keep the injection button pressed all the way in. Slowly count to 10 before you withdraw the needle from the skin. This ensures that the full dose will be delivered.

Step 6. Remove and discard the needle

Always remove the needle after each injection and store SoloStar without a needle attached.
This helps prevent:

- Contamination and/or infection,
- Entry of air into the insulin reservoir and leakage of insulin, which can cause inaccurate dosing.

A. Put the outer needle cap back on the needle, and use it to unscrew the needle from the pen. To reduce the risk of accidental needle injury, never replace the inner needle cap.

- If your injection is given by another person, special caution must be taken by this person when removing and disposing the needle. Follow recommended safety measures for removal and disposal of needles (e.g. a one handed capping technique) in order to reduce the risk of accidental needle injury and transmission of infectious diseases.

B. Dispose of the needle safely, as instructed by your healthcare professional.

C. Always put the pen cap back on the pen, then store the pen until your next injection.

Storage Instructions

Please check the reverse (insulin) side of this leaflet for instructions on how to store SoloStar.

If your SoloStar is in cool storage, take it out 1 to 2 hours before you inject to allow it to warm up. Cold insulin is more painful to inject.

Discard your used SoloStar as required by your local authorities.

Maintenance

Protect your SoloStar from dust and dirt.

You can clean the outside of your SoloStar by wiping it with a damp cloth.

Do not soak, wash or lubricate the pen as this may damage it.

Your SoloStar is designed to work accurately and safely. It should be handled with care. Avoid situations where SoloStar might be damaged. If you are concerned that your SoloStar may be damaged, use a new one.